REMARKS

Status of the Claims.

Claims 51, 66, and 294-313 are pending with the entry of this amendment, claims 60-65, 67, 68, 74, 75, and 293 being canceled without prejudice, and claims 294-312 being added herein. Claims 51 and 66 are amended herein. All pending claims have been amended to recite or incorporate the element that "said polypeptide is free of at least one component naturally occurring with Hsp47." Support for this amendment is found at least at page 11, lines 26-32, which sets forth a definition of "isolated," which was recited or incorporated in all previously pending claims. The phrase "said polypeptide prevents or reduces such damage" incorporates an element recited previously in claim 60. New claim 312 finds support at least at page 16, lines 25-26. Support for new claim 313 was acknowledged by the Examiner at page 8 of the Office Action. Support for the remaining amendments is as explained below, and thus, the amendments add no new matter.

Claim Structure and Support.

Upon review of the extensive prosecution history in this application, Applicant understands that the Examiner believes that the present application enables and adequately describes only the use of two polypeptide species, SEQ ID NOs: 3 and 6, in the claimed method. Applicants believe that this view gives insufficient weight to the high level of skill in the art of protein chemistry, as well as the guidance provided in the specification. Nevertheless, as Applicants wish to expedite allowance of this application, Applicants have amended the claims to relate to more specific embodiments and have provided a detailed and specific rationale as to why these embodiments are fully enabled and adequately described in the specification.

Applicants have also substantially revised the claims in an effort to render the claim structure more readily comprehended. The pending claims recite the embodiments of the invention in three ways. First, claims 51, 66, and 294-297 recite that "the amino acid sequence of said polypeptide ***consists essentially of***" a specific peptide sequence(s). Claim 313 depend from claims within this group and recites that "the polypeptide has greater than 95% sequence identity to the human HSP47 polypeptide sequence presented as SEQ ID NO:6." Second, claims 298-304 recite "the amino acid

sequence of said polypeptide ***consists of***" a specific peptide sequence(s). Finally, claims 305-310 recite mammalian Hsp47s, and claim 311 recites chicken Hsp47.

The starting point for the first two sets of claims ("consisting essentially of" claims and "consisting of" claims) is the 9-residue Hsp consensus sequence appearing in Figure 2 of the specification. The next three claims recite the specific 9-residue sequences from human; from rat, mouse and hamster (these species share the same sequence); and from chicken. Support for these specific sequences is found in Figure 2. ***Notably, claim 299 recites the SEQ ID NO:3 embodiment, which the Examiner has indicated is enabled and adequately described in the specification.*** The final two claims in each of these claim sets are drawn to multimers of the sequences recited in the preceding claims. Support for multimers is found the specification at least at page 16, line 31 - page 17, line 1.

The broadest claim in the third claim set (claim 305) recites mammalian Hsp47, which finds support in the specification at least at page 8, lines 13-21. The following claims recite human (claims 306 and 307), mouse (306 and 308), rat (306 and 309), hamster (306 and 310), and chicken Hsp47 (311). ***The Examiner has indicated that "the human Hsp47 polypeptide sequence presented as SEQ ID NO:6" (see claim 307) is enabled and adequately described in the specification.*** Support for rat and chicken Hsp 47 is found at least at page 8, lines 17-18 of the specification. Support for mouse and hamster Hsp47 is at least inherent in page 8, lines 13-21, taken with Figure 2.

Claim Objections.

Claim 65 was objected to as it was unclear how it differed from claim 63. Office Action, page 2. This objection is moot as both claims have been canceled.

35 U.S.C. § 112, Second Paragraph.

Claims 62-65, 67, 74, and 75 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite on various grounds. Office Action, page 2. This rejection is moot in light of the cancellation of these claims.

35 U.S.C. §112, First Paragraph, Enablement.

Claims 51, 60-68, 74, 75, and 293 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Office Action, page 3. In particular, the Examiner alleged that the specification is not enabling for any polypeptides other than those of SEQ ID NOS: 3 and 6. Applicants respectfully traverse. The rejection is discussed below with respect to all of the new claims to establish that they are free of the rejection.

"Consisting essentially of" Claims 51, 66, 294-297, and 313

Claim 51 recites:

> A method for reducing or preventing immune-mediated damage to cells, tissues or organs comprising contacting a cell, tissue or organ with an immunoprotective amount of a polypeptide, wherein the amino acid sequence of said polypeptide consists essentially of: AVLSAX_4X_5LR (SEQ ID NO:1), wherein X_4 is D or E, X_5 is K or Q, and said polypeptide is free of at least one component naturally occurring with HSP47, wherein the immune-mediated damage is caused by lymphocytes, NK cells or NK-like cells, and said polypeptide prevents or reduces such damage.

M.P.E. P. § 2111.03 states that the "transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). This partially closed claim reads on polypeptides that can include additional amino acid sequences on either side of the recited sequence. However, any additional amino acid sequences must not alter the basic and novel characteristic of the recited sequence, namely its immunoprotective effect. Applicants appreciate that this claim theoretically encompasses a very large genus of polypeptides. However, Applicant submits that at claim of this scope is absolutely necessary to adequately protect Applicant's pioneering invention. More specifically, Applicant was the first to demonstrate that Hsp47 had the ability to protect cells, tissues, and organs from immune-mediated damage is caused by lymphocytes, NK cells or NK-like cells. Applicant also showed that this immunoprotective effect was attributable to a 9-residue domain in human Hsp47. Protein chemists appreciate that proteins typically consist of discrete domains that mediate specific functions. Some domains are discontinuous, meaning that multiple sequences, separated from one another in the primary sequence, come together when the

protein folds to form the active domain. Applicant has demonstrated that this is not the case for the 9-residue immunoprotective motif from human Hsp47, which is a continuous sequence that is sufficient for activity. Accordingly, one of skill in the art would reasonably expect that this immunoprotective motif would work in a wide variety of protein contexts. Applicant notes the Examiner's statement that "some fragments of SEQ ID NO:6, e.g., fragments *comprising* SEQ ID NO:3 do *not* function in the claims method (deletion mutant 2)." Office Action, page 4. This overstates Applicant's data on deletion mutant 2, which is shown in Figure 15C. In this study, Applicant tested three deletion mutants of human Hsp47 for specific lysis in a ^{51}Cr release cytytoxicity assay; the lysis observed in the presence of each deletion mutant was compared with the lysis observed in the absence of any added Hsp47 polypeptide. Deletion 1 lacked the RDEL domain of Hsp47 and reduced lysis by 40%. Deletion 2 lacked the serpin and RDEL domains and reduced lysis by 20%. Deletion 3 lacked the C-terminal 150 amino acids of Hsp47 and was as effective as deletion 1 (40%) in reducing lysis. *See* Applicant's specification, page 4, line 24 - page 45, line 4 and Fig. 15C. Each of these deletion mutants comprised the 9-residue SEQ ID NO:3. Notably, all three polypeptides were immunoprotective and would, contrary to the Examiner's statement, function in the claimed method. At page 29, lines 19-24 of the specification, Applicants stated:

> In ^{51}Cr-release assays, deletion of the serpin domain let to loss of function of the affected truncation mutants. However, as further deletions of the gene re-established full function to the smaller truncated Hsp47 mutants, expressing then little more that the HLA-A2-consensus region, we assume that the loss of function of the C-terminal truncation of Hsp47's serpin domain causes a conformational change in the protein which normalizes with further truncation.

One of skill in the art reading this passage in connection with Fig. 15C, would appreciate that the phrase "loss of function" referred to a reduction in activity, not to a total loss of function.

The Examiner also objected that the "specification fails to even disclose how the fragment of SEQ ID NO:3 was arrived at." Office Action, page 4. However, the specification discloses that this sequence corresponded to the HLA-A2 homology region, which was present in the deletion 3, which was the smallest deletion mutant disclosed. *See* Example 8. Applicant demonstrated that a peptide having SEQ ID NO:3 was sufficient for immunoprotection. *See* Fig. 12. Accordingly, Applicant has established that this sequence, by itself, or in the context of three different deletion

mutants and full-length Hsp47 is immunoprotective. The specification is devoid of any example in which this sequence was not immunoprotective. Accordingly, one of skill in the art would expect that the disclosed immunoprotective domain would function in the presence of additional amino acid sequences on either side of the domain.

Applicant assumes that the enablement rejection is not based on any difficulty associated with making polypeptides to the full extent of the claims, as the production of a polypeptide of any desired sequence using synthetic or recombinant techniques was well within the level of skill in the art at the time the priority application was filed. It may be that the disclosed immunoprotectice domain will not function in the context of particular polypeptides. However, such polypeptides are excluded from all pending claims, which require that "said polypeptide prevents or reduces such [immune-mediated] damage." Rather, as Applicant understands the rejection, the Examiner contends that it would be undue experimentation to one of skill in the art to test alternative polypeptides to those disclosed in the specification. However, Applicant's specification discloses a ^{51}Cr Release Cytotoxicity Assay at page 40, line 10 - page 45, line 4, which was employed to determine whether the disclosed Hsp47-related polypeptides were immunoprotective

The Examiner notes that "[g]iven that said methods comprise no particular expectation of success with any particular test candidate, said methods are not enabled unless the test pool is limited." Applicants know of no authority for this statement and note that is contradictory to the controlling precedent, *In re Wands,* 8 USPQ2d 1400 (1988). *In re Wands* concerned an enablement rejection of immunoassay methods using high-affinity IgM monoclonal antibodies. Indeed the sole issue in *Wands* was whether it would require undue experimentation to produce high-affinity IgM monoclonal antibodies in the absence of a deposit of such antibodies. *Wands*, at 1404. In *Wands*, the Federal Circuit first pointed out that:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the inventions must not be undue experimentation. "[T]he key word is 'undue,' not 'experimentation.'"

Id. (citations omitted).

After reviewing the evidence, the Federal Circuit reversed the enablement rejection concluding:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics.

Id. at 1406-07. In *Wands* there was no limitation on the test pool. An infinite number of hybridomas could be made to yield an infinite number of monoclonal antibodies, which could be screened *ad infinitum* to identify antibodies that had the desired affinity and could therefore be used in the claimed method. Nevertheless, the court found the claims enabled because, in *Wands*, the experimentation was the type of experimentation that practitioners were willing to carry out to obtain an antibody with the desired characteristics. Applicants submit that the same is true here and that, as in *Wands*, a single experiment is need not be the screening of a single polypeptide for immunoprotective activity, but instead, could be the screening of a series of polypeptides, which could even be ordered from a protein synthetic service.

Given that the specification enables such studies, Applicant submits that consisting "essentially of" claims are entirely commensurate with what Applicant has placed into the public domain. Conversely, limiting the protection for Applicant's invention to the specifically exemplified polypeptides renders the invention easy to "design around," as a competitor seeking to avoid infringement would merely have to routinely screen and identify additional polypeptides including the recited immunoprotective motif. The unfairness of requiring such a limitation has been recognized by the courts. As stated by the CCPA:

> To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

In re Goffe, 191 USPQ 429, 431 (CCPA 1976).

Applicants note that the broadest "consisting essentially of" claim, claim 51 defines an immunoprotective motif as the genus: AVLSAX$_4$X$_5$LR (SEQ ID NO:1), wherein X$_4$ is D or E, X$_5$ is K or Q. This genus consists of only four members, one of which is the exemplified human motif (SEQ ID NO:3), and another of which is the corresponding motif, as found in Hsp47 from other species, namely the motif from rat, mouse, and hamster (AVLSAEKLR [SEQ ID NO:1]), which is specifically recited in claim 294. Applicants submit that one of skill in the art would reasonably expect that the rat/mouse/hamster motif, which differs from the human motif in only one residue (AVLSAEKLR for rodent versus AVLSAEQLR for human), would have the same immunoprotective activity as the human motif. Furthermore, the specification teaches an assay that could be used to test the other two sequences within the genus to confirm their activity.

Claim 295 recites polypeptides wherein the amino acid sequence consists essentially of the chicken motif (AVLSADKLN [SEQ ID NO:9]). One of skill in the art would reasonably expect that this motif would be immunoprotective because it is the sequence in the chicken ortholog of human Hsp47 that corresponds to the immunoprotective motif, and orthologs are reasonably expected to have similar structure-function relationships.

Claims 296 and 297 relate to multimers of the specifically recited genus of claim 51 or species of claims 294 and 295. One of skill in the art reasonably expects that, when a short motif has been demonstrated to have a particular activity, including multiple copies of that motif in a polypeptide sequence will not abolish that activity.

Claim 312 further limits the scope of the "consisting essentially of" claims by reciting that the amino acid sequence of the polypeptide, in addition to having one or more of the recited immunoprotective motifs, must also have "greater than 95% sequence identity to the human HSP47 polypeptide sequence presented as SEQ ID NO:6." This claim limits the amount of deviation from SEQ ID NO:6 to no more than 20 amino acids. While Applicant appreciates that this claim encompasses a large genus, it is not an unlimited one. Accordingly, this claim directly addresses the Examiner's statement that

"said methods are not enabled unless the test pool is limited." Office Action, page 5. While Applicant disagrees with this statement, Applicant notes that it implies that "said methods are enabled if the test pool is limited." And Applicant believes that this affirmative statement is correct where, as here, the specification provides an assay for testing the members of the test pool.

Therefore, withdrawal of the enablement rejection of claims 51 and 66 is respectfully submitted. Applicants submit that claims 294-297 and 313 are free of the rejection.

"Consisting of" Claims 298-304

Claims 298-304 recite that the polypeptide "the amino acid sequence of said polypeptide consists of" the above-described genus ($AVLSAX_4X_5LR$ [SEQ ID NO:1], wherein X_4 is D or E, X_5 is K or Q) or specifically recited sequences corresponding to the human, rodent, and chicken motifs, as well as multimers thereof. Claims 298-302 are closed to the addition of amino acid sequences on either side of the recited sequences, and therefore these claims relate to four specific peptides, one of which has been reduced to practice, i.e., SEQ ID NO:3 (recited in claim 299), and two of which are merely species variants of SEQ ID NO:3. Claims 303 and 304 relate to multimers of the recited sequences, but are otherwise closed to the addition of other amino acid sequences. Any of the sequences are, as described above, easily made and tested, following the guidance in the specification. The Examiner has already indicated that the specification enables SEQ ID NO:3, and thus claim 299 is clearly free of this rejection. Applicants submit that claims 298, and 300-304 are also clearly free of the rejection.

Claims 305-311 - Mammalian Hsp47s and Chicken Hsp47

Claims 305-310 recite mammalian Hsp47s, and claim 311 recites chicken Hsp47. The Examiner has already acknowledged that the use, in the claimed method, of the human sequence (SEQ ID NO:6) is enabled. This sequence is set forth in claim 307, and this claim is therefore free of the enablement rejection.

Claims 308-310 recite the mouse, rat, hamster, and chicken Hsp47s, respectively. Applicants' specification teaches:

> The entire human Hsp47 cDNA sequence is set forth in Figure 1A. It is within the level of skill of the art to prepare purified recombinant or synthetic

> Hsp47 cDNA and polypeptides from vertebrates such as mammals and employ those non-human cDNAs and Hsp47 polypeptides in the subject compositions and methods. For example counterparts to human Hsp47 are known in chicken and rat.

Applicant's specification, page 8, lines 13-18. Figure 2 of the specification shows the immunoprotective motif from mouse, rat, hamster, and chicken Hsp47s, making it clear to one of skill in the art that these specific Hsp47s could be employed in the methods of the invention. The mouse, rat, hamster, and chicken Hsp47 would reasonably be expected to have similar immunoprotective activity to the human Hsp47 because orthologs are identified as such on the basis of similar structure and function. Accordingly, Applicant submits that one of skill in the art, following the teachings of the specification, could practice the claimed method with mouse, rat, hamster, or chicken Hsp47. Accordingly, claims 308-310 are also free of the enablement rejection.

Claim 312 depends from the above-discussed independent claims and is therefore free of the enablement rejection for at least the reasons discussed above.

In view of the foregoing, undue experimentation is not required to practice the presently claimed invention. Accordingly, withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph, is respectfully requested

35 U.S.C. §112, First Paragraph, Written Description.

Claims 51, 60-68, 74, 75, and 293 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the written description requirement. Office Action, page 6. The rejection is moot as to canceled claims 60-65, 67, 68, 74, 75 and 293. Applicants respectfully traverse with respect to claims 51 and 66. The new claims are also discussed below to establish that these are free of the rejection.

The rationale underlying the rejection is that "the claims [allegedly] encompass the use of an essentially unlimited genus of variant proteins and peptides, none of which have been disclosed." *Id.* Applicants appreciate that a written description issue may arise where claims recite an unlimited genus and the specification discloses a limited number of exemplified species. However, the fact that claim encompasses an unlimited genus is cannot be dispositive because ***every*** "comprising" claim encompasses an unlimited genus, and the Patent Office routinely issues comprising claims.

Furthermore, the statement that the specification does not disclose any variant proteins is not correct. As discussed above, the specification discloses three deletion mutants that are, of course, variants of the full-length Hsp47 sequence.

The Examiner also states that in "the instant case the proteins and peptides are described by function only, no meaningful structural characteristics are disclosed." *Id.* This statement is not true with respect to the pending claims, as discussed in detail below.

"Consisting essentially of" Claims 51, 66, 294-297, and 313

Claim 51 recites:

> A method for reducing or preventing immune-mediated damage to cells, tissues or organs comprising contacting a cell, tissue or organ with an immunoprotective amount of a polypeptide, wherein the amino acid sequence of said polypeptide consists essentially of: AVLSAX_4X_5LR (SEQ ID NO:1), wherein X_4 is D or E, X_5 is K or Q, and said polypeptide is free of at least one component naturally occurring with HSP47, wherein the immune-mediated damage is caused by lymphocytes, NK cells or NK-like cells, and said polypeptide prevents or reduces such damage.

As stated in *Union Oil Co. of California v. Atlantic Richfield Co.*, 54 USPQ2d 1227 (CAFC 2000), ***the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed***.'" *Id.* at 1232 (emphasis added; citation omitted). The primary purpose of this requirement is to ensure that the specification clearly conveys to one skilled in the art what the applicant regarded as his or her invention when the application was filed. This requirement serves the public policy of limiting the ability of an applicant to later claim subject matter that, while enabled by the specification, was not identified in the specification as the applicant's invention. Thus, as the Federal Circuit reiterated in *Purdue Pharma L.P. v. Faulding Inc.*, "[a]dequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Purdue Pharma L.P. v. Faulding Inc.,* 56 USPQ2d 1481, 1487 (Fed. Cir. 2000) (quoting *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) and *Rengo Co. v. Molins Mach. Co.*, 211 USPQ 303, 321 (3d Cir. 1981)).

At issue in the present case is whether Applicant's specification adequately describes a genus of polypeptides, "wherein the amino acid sequence of said polypeptide consists essentially of: $AVLSAX_4X_5LR$ (SEQ ID NO:1), wherein X_4 is D or E, X_5 is K or Q."

According to M.P.E.P. §2163, the "written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species." M.P.E.P. § 2163 (Rev. 3, August 2005), page 2100-182. However, the M.P.E.P. acknowledges that "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *Id.* at page 2100-183. Rather, "[s]tisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." *Id.* In the present case, the specification sets forth, and the claims recite, the common attributes of the member of the genus, namely (1) the amino acid sequence defined by the formula: $AVLSAX_4X_5LR$ (SEQ ID NO:1), wherein X_4 is D or E, X_5 is K or Q (four different sequences), and (2) the ability to reduce or prevent "damage is caused by lymphocytes, NK cells or NK-like cells."

The rejection is based, in part, on the Examiner's characterization of the claimed genus as "essentially unlimited," and that the specification, in the Examiner's view, describes two exemplified species. Office Action, page 6. However, the case law makes clear that the determination that a genus is big and the number of species exemplified in the specification is relatively small is, by itself, an insufficient basis for a rejection for lack of written description. *In re Rasmussen*, 650 F.2d 1212 (CCPA 1981), is cited in the M.P.E.P. for the proposition that "there may be situations where one species adequately supports a genus." M.P.E.P. § 2163 (Rev. 3, August 2005), page 2100-182. In this case, the C.C.P.A. reversed a rejection for lack of written description on the ground that disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand it was unimportant how the layers were adhered, so long as they were adhered. *Id.* Applicant submit that *Rasmussen* on point because, in the present case, one skilled in the art reading the specification would understand that the recited sequence mediates the recited immunoprotective activity. The specification demonstrates that the human immunoprotective motif is sufficient, by itself, for this activity and that this motif functions in full-length Hsp47 and in three deletion mutants thereof. The presence of

additional amino acid sequences beyond the recited sequence is unimportant, so long as the immunoprotective activity of the recited sequence is not abolished.

In *Rasmussen*, the court stated:

> A hypothetical situation may make our point clear. If the original specification of a patent application on the scales of justice disclosed only a 1-pound "lead weight" as a counterbalance to determine the weight of a pound of flesh, we do not believe the applicant should be prevented, by the so-called "description requirement" of the first paragraph of § 112, or the prohibition against new matter of § 132, from later claiming the counterbalance as a "metal weight" or simply as a 1- pound "weight," although both "metal weight" and "weight" would indeed be progressively broader than "lead weight," including even such an undisclosed, but obviously art-recognized equivalent, "weight" as a pound of feathers. The broader claim language would be permitted because the description of the use and function of the lead weight as a scale counterbalance in the whole disclosure would immediately convey to any person skilled in the scale art the knowledge that the applicant invented a scale with a 1-pound counterbalance weight, regardless of its composition.

Rasmussen, at 1215. This case makes it clear that the description requirement inquiry requires more than simply counting exemplified species and comparing this number to the size of the claimed genus. Indeed, the court explicitly stated: "***that a claim may be broader than the specific embodiment disclosed in the specification is in itself of no moment***." *Id.* (emphasis added). In the present application, the specification describes the structure of the claimed polypeptides, as well as their use and function as an immunoprotectant. The present specification goes farther than that in the *Rasmussen* case in that the present specification describes five species (as opposed to one in *Rasmussen*) and explicitly describes the claimed genus (which the *Rasmussen* specification did not do). Applicant submit that this description would immediately convey to any person skilled in the art the knowledge that the Applicant invented a polypeptide "wherein the amino acid sequence of said polypeptide consists essentially of: $AVLSAX_4X_5LR$ (SEQ ID NO:1), wherein X_4 is D or E, X_5 is K or Q."

In addition, as stated in the M.P.E.P., the "written description requirement for a claimed genus may be satisfied ***"by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed***

correlation between function and structure, or by a combination of such identifying characteristics." M.P.E.P., page 2100-182 (emphasis added). The claims have been amended to recite that the claimed possess a structural feature and an associated functional characteristic, both of which are described in Applicant's specification. In particular, the claims recite that the peptides must include one of only four amino acid sequences that mediate immunoprotection. Furthermore, as noted above, the specification describes a method that can be used to determine whether a particular polypeptide is immunoprotective. Thus, consistent with the test articulated in *Union Oil Co. of California v. Atlantic Richfield Co.*, the description clearly allows persons of ordinary skill in the art to recognize that the Applicant invented what is claimed. *Id.* at 1232. Accordingly, the specification clearly conveys to one skilled in the art what Applicant regarded as his invention when the application was filed.

Support for this position can be found in any number cases, such as, for example, *In re Robins*, 166 USPQ 552 (CCPA 1970), where the court stated:

> If the examiner and/or the board intended a rejection under the first paragraph of § 112, it must be reversed inasmuch as the specification contains a statement of the Applicant's invention which is a broad as Applicant's broadest claims . . . .
>
> Both the examiner and the board seem to have taken the position that in order to "justify," as the examiner said, or to "support," as the board said, broad generic language in a claim, the specification must be equally broad in its naming, and use in examples, of representative compounds encompassed by the claim language. This position, however, misapprehends the proper function of such disclosure. Mention of representative compounds encompassed by generic claim language clearly is not required by § 112 or any other provision of the statute. But, when no explicit description of a generic invention is to be found in the specification (which is not the case here) mention of representative compounds may provide an implicit description upon which to base generic claim language . . . Similarly, representative examples are not required by the statute and are not an end in themselves. Rather, they are a *means* by which certain requirements of the statute may be satisfied.

In re Robins, at 555. The description requirement inquiry is intensely fact-specific (*see Union Oil*, at 1232), and the facts of the present application are similar to those in *Robins* in that the present application contains generic description to support generic claim language. The present application

differs from the *Robins* application in that the present application discloses representative species, which the *Robins* application did not. Thus, the present application includes the same type of description that was found, in *Robins,* to satisfy the description requirement. Furthermore, the present application includes additional description not found in the *Robins* application, namely, the specific description of multiple species. The Patent Office's own guidelines in the M.P.E.P., discussed above, indicate that this is another explicitly approved means of satisfying the § 112, written description requirement. Accordingly, Applicant submit that the specification contains more than adequate written description for the invention recited in the pending claims.

Finally, with respect to the "consisting essentially of" claims, Applicant notes that claim 313 recites that the amino acid sequence of the polypeptide, in addition to having one or more of the recited immunoprotective motifs, must also have "greater than 95% sequence identity to the human HSP47 polypeptide sequence presented as SEQ ID NO:6." This claim limits the amount of deviation from SEQ ID NO:6 to no more than 20 amino acids and therefore also limits the size of the genus. Accordingly, claim 313 is free of the Examiner's objection that the genus is essentially unlimited.

Withdrawal of the written description rejection under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

"Consisting of" Claims 298-304

Claims 298-304 recite that"the amino acid sequence of said polypeptide consists of" the above-described genus (AVLSAX_4X_5LR [SEQ ID NO:1], wherein X_4 is D or E, X_5 is K or Q) or specifically recited sequences corresponding to the human, rodent, and chicken motifs, as well as multimers thereof. Claims 298-302 thus relate to four specific peptides, one of which has been reduced to practice, i.e., SEQ ID NO:3 (recited in claim 299), and two of which are merely species variants of SEQ ID NO:3. Claims 303 and 304 relate to multimers of the recited sequences, but are otherwise closed to the addition of other amino acid sequences. Any of the sequences are, as described above, easily made and tested, following the guidance in the specification. The Examiner has already indicated that the specification adequately describes SEQ ID NO:3, and thus claim 299 is clearly free of the written description rejection. Applicants submit that claims 298, and 300-304 are also clearly free of this rejection.

Claims 305-311 - Mammalian Hsp47s and Chicken Hsp47

Claims 305-310 recite mammalian Hsp47s, and claim 311 recites chicken Hsp47. The Examiner has already acknowledged that the use, in the claimed method, of the human sequence (SEQ ID NO:6) is enabled. This sequence is set forth in claim 307, and this claim is therefore free of the description requirement rejection.

Claims 308-310 recite the mouse, rat, hamster, and chicken Hsp47s, respectively. As discussed above, these Hsp47s are described by name in Applicant's specification, and the sequences of the immunoprotective motifs for each of these Hsp47s is given in Fig. 2. These molecules were known prior the filing date of the application, and therefore, the description in the specification is sufficient to allow one skilled in the art to distinguish these molecules from others in the art and to conclude that Applicant invented a method that could employ these molecules, as well as the exemplified human Hsp47.

Claim 305 recites the use of "mammalian" Hsp47. Applicant notes that this genus is large. However, the specification shows that four mammalian Hsp47s (human, mouse, rat, and hamster) have immunoprotective motifs that vary from one another by only 1 amino acid residue. Given that Hsp47s from species as divergent as humans and rodents share this common characteristic, Applicant submits that one of skill in the art would appreciate that Applicant invented the use of mammalian Hsp47s in the claimed method. Accordingly, claims 305-311 are free of the written description rejection.

Claim 312 depends from the above-discussed independent claims and is therefore free of the written description rejection for at least the reasons discussed above.

35 U.S.C. § 102/103.

Claims 51, 60-68, 74, 75, and 293 stand rejected under 35 U.S.C. §102(b) as anticipated by Hoppe *et al.* (1995) *Upregulation of a 46 kDa Collagen Binding Protein Correlates With Protection of HUVEC Cells In Vitro Against Cytolysis By CD3+56+CTL and IL-2 Stimulated Natural Killer Cells, Blood,* 86 (Suppl 1) 322A (abstract 1277). Office Action page 7. Applicants respectfully traverse.

The Examiner states that "Hoppe et al. teaches a method for reducing immune-mediated damage to cells, tissues, or organs comprising contacting a cell, tissue or organ with an

immunoprotective amount of a polypeptide comprising Hsp47." Office Action, page 7. This statement is incorrect. Hoppe teaches that "treatment of HUVEC target cells with Brefeldin A (BFA) protects them from CIK and IL-2 stimulated NK cell mediated cytotoxicity." Hoppe further teaches that treatment "of HUVEC with BFA induces cell membrane expression of a glycoprotein of 46 Kd M_r." By contrast, all of the pending claims require the administration of the recited polypeptide, "wherein said polypeptide is free of at least one component naturally occurring with HSP47." Administering a polypeptide under such circumstances is clearly different from administering drug, in this case, an antibiotic, which has myriad effects. In addition to upregulating the disclosed 46 kD glycoprotein,

> BFA treatment has been reported to lead to a complex series of changes in treated cells, via selective intoxication of a G-protein responsible for protein transport between cis- and medial golgi compartments. The transport block results in a backing-up of secretion directed proteins into an enlarging ER system and leads finally to the fusion of the cis-golgi compartements with the ER. . . . The enlargement of the ER compartment increases the synthesis of ER resident proteins. ER resident proteins are characterized by a C-terminal four amino acid "KDEL" or "RDEL"-ER retention signal. Examples of such ER-resident proteins are Hsp47, calreticulin, GRp78 and Grp94. . . . Enlargement of the ER by BFA treatment perturbs the cellular Ca^{2+} homeostasis and leads to inactivation of the KDEL/RDEL receptor. . . . ER resident proteins . . . thus become freely secreted.

Applicant's specification, page 25, line18 - page 26, line 5. Thus, BFA upregulates an entire class of proteins (ER resident proteins) via a complex series of changes, including changes in cellular architecture and Ca^{2+} homeostasis. Hoppe teaches that the disclosed 46 kD glycoprotein is correlated with immunoprotection. Hoppe does not teach that this protein is causative. More specifically, it is impossible to know, from reading Hoppe, whether the 46 kD glycoprotein could mediate immunoprotection. Furthermore, it is unclear from Hoppe whether the 46 kD glycoprotein, if causative, is sufficient for immunoprotection. Thus, Hoppe does not rule out the possibility that another ER resident protein, that is co-induced with the 46 kD glycoprotein, is responsible, or required, for immunoprotection. Accordingly, Hoppe provides no reasonable expectation that the 46 kD could be separated from at least one other component present in the cell with it and employed to immunoprotect cells, tissues, or organs.

The Examiner cites the last sentence of Hoppe, which states that the "potential of p46 to prevent vascular leak syndrome associated with AI or CIK anti-tumor purging protocols is currently under investigation in a SCID/hu in-vivo model." Office Action, page 7. This statement makes it clear that any possible immunoprotective effect of p46 was in question.

The Examiner notes that the "reference teaches the purification of Hsp47." *Id.* However, the reference does not indicate that the purified p46 was actually contacted with cells, tissues, or organs. The vague statement indicating that the "potential of p46 to prevent vascular leak syndrome . . . is currently under investigation" does not indicate that the "contacting" step of the claimed method had actually been carried out. In the absence of any evidence that purified p46 was contacted with cells, tissues, or organs, Hoppe cannot anticipate the claimed method. Nor is the claimed method obvious in light of Hoppe because the reference fails establish that p46, by itself, mediates, and is sufficient for, immunoprotection. In the absence any such teaching or suggestion, Hoppe cannot provide a reasonable expectation that the claimed method would be successful.

Furthermore, all of the pending claims recite sequences that Hoppe fails to teach or suggest. Applicant recognize that the Examiner may properly rely base a § 102 rejection on an inherent characteristic, such as an amino acid sequence, but, for the reason noted above, a § 102 rejection cannot be maintained because Hoppe fails to teach that the recited "contacting" step was actually carried out using purified p46. Thus, the only possible art-based rejection would be one under § 103. However, a § 103 rejection cannot generally be based on an inherent property, such as amino acid sequence, because "[o]bviousness cannot be predicated on what is unknown." *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed Cir. 1993) (citing *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966)). For this additional reason, the claimed method is patentable over Hoppe.

Accordingly, the rejection of claims 51 and 66 under 35 U.S.C. §102(b) should be withdrawn.

A number of the new claims recite additional distinctions over Hoppe. In particular, claims 296 and 297 relate to multimers. Hoppe contains no teaching or suggestion regarding multimers of p46.

"Consisting of" claims 298-304 relate to specific 9-residue amino acid sequences that define the immunoprotective domain discovered by Applicant, and claims 303 and 304 relate to multimers of this domain. Any teaching of Hoppe regarding the activity of the disclosed 46 kD

polypeptide cannot be extrapolated to a 9-residue amino acid sequence, because Hoppe contains no hint as to what domain(s) of p46 might mediate its activity. Indeed, because many protein domains are discontinuous, it was not at all clear that ***any*** 9-residue sequence in p46 would be immunoprotective. Claims 298-304 are thus clearly patentable over Hoppe. Within this group of claims, claim 299 recites SEQ ID NO:3. As the Examiner previously acknowledged that the use of this sequence was both enabled and adequately described, Applicant respectfully points out the all rejections of this claims should be withdrawn, and claim 299 should be allowed.

CONCLUSION.

In view of the foregoing, Applicant believes that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicant requests a telephone interview with the Examiner, as Applicant believes that an interview may facilitate the Examiner an Applicant reaching agreement regarding allowable subject matter.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4161.

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